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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,593	12/05/2001	Katherine S. Bowdish	1087-2	3532

7590

02/14/2005

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EXAMINER

HELMS, LARRY RONALD

ART UNIT

PAPER NUMBER

1642

DATE MAILED: 02/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.		Applicant(s)	
	10/006,593		BOWDISH ET AL.	
	Examiner		Art Unit	
	Larry R. Helms		1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 December 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23,36,44,45,85-92 and 96-99 is/are pending in the application.
- 4a) Of the above claim(s) 17,20,21,91 and 92 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-16,18,19,22,23,36,44,45,85-90 and 96-99 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>8/18/03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The request filed on 12/13/04 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 10/006,593 is acceptable and a RCE has been established. Claims 1-23, 36, 44-45, 85-92, 96-99 are pending. An action on the RCE follows.

2. NOTE: It is noted that in the response to the restriction requirement that an election of SEQ ID NO:2 was elected.

The response filed 11/24/03 states that claim 18 has been amended to recite comprising SEQ ID NO:1 and therefore embraces SEQ ID NO:2 which is essentially SEQ ID NO:1 having an additional amino acid, proline at one end. Since SEQ ID NO:2 is SEQ ID NO:1 with a proline at the end and some claims encompass the TPO mimetic with a proline at the end, SEQ ID NO:1 will be examined with SEQ ID NO:2, wherein SEQ ID NO:2 is the TPO mimetic with a proline at the end. No other sequences will be examined at this time.

3. Claims 17, 20-21, 91-92 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. This Office Action contains NEW GROUNDS of rejections.

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6. Claims 1, 44, 86, 96, 99 have been amended.
7. Claims 1-16, 18-19, 22-23, 36, 44-45, 85-90, 96-99 are under examination.

Information Disclosure Statement

8. The Information Disclosure Statement filed 7/19/02 has been considered in part. All US Patents listed on the IDS have been considered, however, all other references were not considered because copies of the references were not in the file. The examiner apologizes for any inconvenience but requests that copies of the references be supplied and the references will be considered at that time.

Rejections Withdrawn

9. The rejection of claims 1-16, 19, 22-23, 36, 90, 96-98 under 35 U.S.C. 112, first paragraph is withdrawn in view of the amendments to the claims.
10. The rejection of claims 1-16, 19, 22-23, 36, 44-45, 85-90, 96-99 under 35 U.S.C. 103(a) as being unpatentable over Barbas et al [a] (WO 94/18221, published 8/94) and further in view of Dower et al (WO 96/40750, published 12/96) and Barbas et al [b] (PNAS 92:2529-2533, 1995) and as evidenced by Helms et al (Protein Science 4:2073-2081, 1995) is withdrawn in view of the new grounds of rejections.

Response to Arguments

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11. The rejection of claims 44-45, 85-89 and 99 under 35 U.S.C. 112, first paragraph is maintained.

The response filed 12/13/04 has been carefully considered but is deemed not to be persuasive. The response states that claims 44, 86 and 99 have been amended to recite that the immunoglobulin or fragment exhibits a desirable biological activity (see page 10-11 of response). In response to this argument, due to the indefinite nature of the language added in the amendments (see 112 second paragraph rejection below) the claims do not require the "desired biological activity" to be due to the biologically active peptide and as such the claims encompass adding a sequence to the CDR that does not have to result in any function of the peptide added.

The following are NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

12. Claims 44-45, 85-89, 99 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 44, 86, and 99 and those that depend from these claims are indefinite for reciting "wherein the immunoglobulin molecule or fragment thereof exhibits a desirable biological activity" because the exact meaning of the phrase is not clear. It is not clear what biological activity is contemplated. Is the activity the result of the antibody such as

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Fc mediated response or antigen binding or is the activity the result of the peptide added to the CDRs or some other activity?

Claim Rejections - 35 USC § 103

13. The rejection of claims 1-16, 18-19, 22-23, 36, 44-45, 85-90, 96-99 under 35 U.S.C. 103(a) as being unpatentable over Barbas et al [a] (WO 94/18221, published 8/94) and further in view of Dower et al (WO 96/40750, published 12/96) and Barbas et al [b] (PNAS 92:2529-2533, 1995) and Kini et al (FEBS Letters 375:15-17, 1995).

The claims are summarized as an immunoglobulin or fragment thereof wherein the immunoglobulin or fragment is anti-tetanus toxoid and a human antibody and comprising wherein the residues corresponding to at least a portion of at least one or two CDRs are replaced with SEQ ID NO:2 or SEQ ID NO:1 with a proline added at the N and/or C terminus wherein the fragment is a Fab or full IgG from and the CDR is on a light chain and/or a heavy chain and the CDR is CDR3 and/or CDR1 or CDR2, and the peptide is flanked by a proline at the C terminus and has an amino acid at its N terminus and the flanking sequence is from several two amino acid peptides (claims 86-89) and compositions comprising such.

Barbas et al [a] teach replacing CDRs in a heavy or light chain of an antibody or Fab fragment with biologically active peptides and randomizing the flanking sequences for presenting a biological active peptide in a conformation for binding to a receptor for

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example (see page 5, 8, 17, lines 5-33, page 19-20, page 26-27, 28-29, 53, 144, 149). Barbas et al also teach that adding the peptide RGD by itself to the CDR resulted in no activity because of flanking residues needed to be added to optimize the conformation (see page 84, lines 8-31). Barbas et al [a] does not teach replacing a CDR with an TPO mimetic of SEQ ID NO:2 or SEQ ID NO:1 with proline flanking the sequence (which is SEQ ID NO:2) or the scaffold is the anti-tetanus toxoid antibody. These deficiencies are made up for in the teachings of Dower et al and Barbas et al [b] and Kini et al.

Dower et al teach peptide sequences of TPO that bind the thrombopoietin receptor and SEQ ID NO:2 without the proline at the C-terminus (which is SEQ ID NO:1, see page 26-30 and Table 7 and 9 and specifically page 76, top molecule which comprises SEQ ID NO:1 with cysteines flanking the sequence, and claim 19 which claims the sequence of SEQ ID NO:1 (see last compound)) and the addition of flanking sequences for structural constraints (see page 45, lines 10-14).

Barbas et al [b] teach replacement of CDR3 in the anti-tetanus toxoid antibody with several sequences.

Kini et al teach design of biologically active peptides with proline residues flanking the sequence and the prolines resulted in restricting the conformation and in enhanced activity of the peptides (see entire document).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the anti-tetanus antibody as a scaffold to present SEQ ID NO:2 in one or two CDRs of the heavy or light chain of the antibody.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the anti-tetanus antibody as a scaffold to present SEQ ID NO:2 in one or two CDRs of the heavy or light chain of the antibody because Barbas et al [a] teach antibodies with several peptide sequences replacing the CDRs in an antibody and the molecules bind the target receptor and suggest that other sequences for other receptors would also work in replacing the CDRs (see pages 24-27) and the need to constrain the peptides (see page 28-29). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the anti-tetanus antibody as a scaffold to present SEQ ID NO:2 in one or two CDRs of the heavy or light chain of the antibody because Barbas et al [b] teach replacement in the anti-tetanus antibody of unrelated sequences from that in the CDR and the antibody binds the target and since antibody tertiary structures are homologous one skill in the art would conclude that the anti-tetanus antibody could be used for other sequences to present. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the anti-tetanus antibody as a scaffold to present SEQ ID NO:2 in one or two CDRs of the heavy or light chain of the antibody because Dower et al specifically teach SEQ ID NO:1 and teach peptides that are fusion proteins and the peptides need to be constrained to be active (see page 42, line 10). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the anti-tetanus antibody as a scaffold to present SEQ ID NO:2 in one or two CDRs of the heavy or light chain of the antibody because Kini et al teach that proline residues prevent the

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extension of neighboring secondary structures and thus protect the conformation and integrity of interaction sites (see page 15) and since prolines limit the flexibility around the alpha-carbon atoms, the number of possible conformations would be drastically reduced (see page 16) and the peptides with the prolines resulted in better activity. It would have been obvious to use an antibody as a scaffold to present the TPO peptide because in solution peptides can be a random configuration and the scaffold constrains the peptide and presents it in a conformation that is better for binding and it would have been obvious to have residues flanking the sequence for presentation and it would have been obvious to use a proline at the C-terminus because as taught by Kini et al it is known in the art that proline residues decrease the conformational flexibility of a peptide and thus would constrain the peptide. In addition, it would have been obvious to place the peptide in a CDR because Barbas et al [a] teach human antibodies have benefits of therapy in vivo in humans for blocking or inhibiting the target and in view of Dower et al who teach that the TPO peptides can be used for therapy, one would have motivation to add the peptide to the antibody CDR.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

14. The response filed 12/13/04 has been carefully considered but is deemed not to be persuasive. The response again seems to argue initially the references separately in stating that Barbas PCT does not teach replacing a CDR with a mimetic of TPO and asks to point to particularity where such a teaching can be found (see page 11) and that

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Barbas PCT generic definition of binding sites encompasses millions of polypeptides and none of the specifically listed material provides motivation to incorporate a TPO or EPO mimetic (see page 11-12). The response argues that Dower fails to disclose incorporating a TPO or EPO mimetic in an immunoglobulin or a flanking sequence (see page 12) and Dower is limited to low molecular peptides and does not suggest incorporation into an immunoglobulin (see page 12) and to cyclize a peptide in no way suggests that the peptide should be inserted into an immunoglobulin (see pages 12-13 of response).

In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to arguments that cyclizing a peptide does not suggest the peptide should be inserted into an immunoglobulin, the cyclization results in constraining the peptide and this is taught in Barbas PCT, Dower, and Kini and because one wants to constrain the peptide either by cyclizing or adding prolines it would be obvious to do such, specifically add prolines as taught by Kini. Adding the peptide into an immunoglobulin CDR is specifically taught or suggested to do so from Barbas because he specifically did such and teaches that other binding peptides can also be added to the CDRs to produce new binding members. Since the peptides as taught by Barbas need to be constrained it would be obvious to add the peptide of Dower to the antibody

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as taught by Barbas and flank the sequence with prolines for conformational constraints as taught by Kini.

The response further states that with respect to claims 18-21, 91, 92, and 96 which have the core sequence of SEQ ID NO:1, the examiner is requested to point out with particularity where there is any motivation to pick this sequence from the millions described by Dower (see pages 13-15). In response to this argument, Dower specifically teaches and claims the exact sequence of SEQ ID NO:1 as stated above in the rejection at specifically page 76, top molecule which comprises SEQ ID NO:1 with cysteines flanking the sequence, and claim 19 which claims the sequence of SEQ ID NO:1 (see last compound). Claims 20-21 and 91-92 these claims are withdrawn because they are directed to non-elected inventions.

The response further states that with regard to the claims that recite biologically active peptide with a proline at the carboxy terminus, none of the applied references teaches or discloses that the presence of a proline at the carboxy terminus of the peptide is useful compared to any other amino acid at that position (see page 15-16 of response). In response to this argument, Kini provides strong motivation and teaches adding a proline residue at the C-terminus of the peptide.

The response further states that claims 86 and 97-99 are to peptides with 2 flanking amino acids and applicant disagree with Barbas PCT that reference to 6 to 50 nucleotides on page 32 teach or suggest 2 flanking amino acids (see page 17 of the response). In response to this argument, a more clearer citation is on page 86 wherein

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the RGD sequence was the peptide sequence and three amino acids on each side were added (see page 86, lines 1-7).

The response further states that with respect to claim 96, the office admitted that neither Barbas PCT or Dower teach a peptide comprising SEQ ID NO:2 and as such claim 96 is allowable (see page 17 of the response). In response to this argument, while neither Barbas PCT or Dower teach alone SEQ ID NO:2, the claim is still rejected under 103 because as stated in the rejection SEQ ID NO:1 is specifically taught in Dower and in view of Kini, one would add a proline to the c-terminus and obtain SEQ ID NO:2. In addition the term comprises is in the claim and as such SEQ ID NO:2 can have additional residues on either side which would be obvious in view of the teaching in the art.

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:00 am to 3:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew, can be reached on (571) 272-0787.


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17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is (571) 273-8300.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832



LARRY R. HELMS, PH.D
PRIMARY EXAMINER